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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,980	09/30/2003	Yaron Iian	Enz-64 (CIP)	9089

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EXAMINER	
HORNING, MICHELLE S	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,980	IIAN ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *2-5, 7--10, 12-42, 46, 53, 55-58, 61-74, 77-96, 98-108, 110-118, 121-123, 129-150, 154-160, 171-177, 183, 185, 187, 189, 197-198, 200-202* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/29/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-126,129-151,154-177,183-185,187,189-191,197,198,200-202 and 205.

Continuation of Disposition of Claims: Claims rejected are 1,6,11,43-45,47-52,54,59,60,75,76,97,109,119,120,124-126,151,157,161-170,184,191 and 205.

DETAILED ACTION

This office action is responsive to communication (RCE) filed 1/28/2008. The status of the claims is as follows: claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 151, 157, 161-170, 184, 191 and 205 are under current examination while the other remaining claims are either canceled or withdrawn from considered because they are drawn to non-elected inventions.

The following rejections have been withdrawn due to claim amendments or filing of a Terminal Disclaimer:

1. 35 USC 102(b) (Anticipated by Taniguchi et al);

2. 35 USC 103 (Unpatentable by Vliet et al and Taniguchi et al);

3. 35 USC 103 (Unpatentable by Vliet et al, Taniguchi et al and Connolly and Cunningham) and

4. Double Patenting (10/375, 906).

Briefly, Applicants have amended the claims so that the scope is narrowed to a mammalian intermediary metabolite. The applied art taught using αGalCer which is isolated from a marine sponge and has yet to be found in mammalian tissues (see Makowska et al, 2000). Arguments with respect to Enablement are addressed below.

Drawings

The drawings are objected to because Figures 16 and 17 depict nothing. Further, it is not clear whether IFN is on the x-axis because the x-axis is labeled as IFN? in Figure 6. Figure 5 provides a horizontal code through the data. Lastly, Figure 11 provides no visible signal of any kind. Corrected drawing sheets in compliance with 37

CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112-NECESSITATED BY AMENDMENTS

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 151, 157, 161-170, 184, 191 and 205 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for modulation of an

immune response related to Hepatitis (at most), does not reasonably provide enablement for treatment of any kind disease associated with inflammatory responses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Enablement is considered in view of the *Wands* factors.

Nature of the invention. The invention is drawn to a method for the treatment of a disease wherein there is an inflammatory immune response comprising administering a mammalian intermediary metabolite to a mammal.

State of the prior art. The prior art teaches the differences in ligand specificity between NKT cells, using multiple ceramides including glucocerebroside or glucosylceramide (see Makowska et al, whole document). Makowska et al teach that αGalCer and other glycolipid variants stimulate V α14+ NKT cells (see Discussion). Also, see page 72 which lists the various ceramides.

Breadth of the claims. The claims are broad, encompassing the treatment of any and all diseases in which an inflammatory response is associated. Applicants have suggested throughout the REMARKS that limiting the claims to a disease associated with an inflammatory response "limits the particular diseases that would be used with the current invention *since many diseases do not involve an inflammatory response* and for most diseases that do involve an inflammatory response, this response is part of the curative process rather than the pathogenesis" (emphasis added). This recitation is noted for reasons of record. ***Applicant is invited to provide references which teach that many diseases do not involve an inflammatory response.***

Working examples. The working examples are specifically directed towards glucocerebroside treatment of a Con A-induced hepatitis model, a colitis model and a model for non-alcoholic steatohepatitis. The working examples provide no parallel towards the successful treatment of inflammatory responses for all possible diseases. Applicants state that the differential diseases "share the common feature of an inflammatory process responsible for the symptoms of the disease". The recitation is noted for reasons of record. In response, the Examiner invites the Applicants to provide further elucidation and point out the support in the instant specification. What common feature? Also, please note that paragraph 48 provides the following recitation: “The treatment of a disease may also result in a change the cytokine responses. Any cytokine in the immune system may be involved in these responses. The change could result in a pro-inflammatory or an anti-inflammatory response. There may also be a pro-inflammatory, and an anti-inflammatory response since certain cytokines may increase and others may decrease, simultaneously.” This recitation is emphasized merely to show that the inflammatory response is complex and can be very different depending on disease. Thus, the cytokine production is not a common ground.

Guidance in the specification. The specification provides little guidance regarding the practice of the methods as claimed. It is not clear what the Applicant is arguing. Applicants state that it is not a requirement for the practice of the invention that all parameters be known for all diseases. In response, something must be known to claim the treatment of all diseases with an inflammatory response and the specification lacks disclosing it.

Predictability of the art. There is none. Diseases lead to differential responses and there can be no predictability in treating them all; see discussion above with respect to differential productions of cytokine provided by the instant specification. The argument is not clear. Applicant provides the following: “many diseases do not involve an inflammatory response at all” and diseases with an inflammatory response is “describing a limited group of diseases” and the specification is drawn to "the common factor that is being treated". Of note, the common factor must not be the differential cytokine response as the instant specification describes in paragraph 48.

Amount of experimentation necessary. It would require years of further research to develop effective therapy for any and all diseases with an inflammatory response. Applicant recites the following: “Applicants respond that it is quite *unrealistic* to state that it would take years to practice the present invention when three separate working examples have actually been disclosed. Furthermore, as described above, Applicants have included limitations in Claim 1 thereby showing that the diseases are restricted to ones that have pathology contributed by immune reactivity and that the mammalian intermediary metabolites used for treatment of the disease are limited to lipids and glycolipids. These limitations are part of the exemplifications of the three disease models described above and as such, create a closer association between the claimed method and the disclosed examples.

In conclusion, Applicants believe that the disclosures provided in the specification of the present invention not only do not necessitate undue experimentation, but also severely

limit the requirement of any additional experimentation to carry out the claimed invention".

In response, it would be "quite unrealistic" to claim a method of treating any and all diseases associated with an inflammatory response. Diseases associated with such a response would include cancer, heart disease, Pelvic Inflammatory Disease, Bowel Disease, many periodontal diseases, allergies and asthma and much more. The specification does not disclose any common feature among any disease that was successfully treated. The three working examples do not demonstrate that their successful treatment would also lead to the successful treatment of all diseases with an inflammatory response. The phrase, diseases with an inflammatory response, fails to describe a limited group of diseases. Further, it is absolutely untrue that many diseases do not involve an inflammatory response. Not one argument is found to be persuasive. Thus, it would take years to develop a method as claimed *if even possible at all*. No argument is found to be persuasive.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75, 97, 109, 119-120, 124-126, 151, 157, 161-168 and 184 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 6610835 (hereinafter as "Liotta").

Liotta et al describe the use of sphingolipid derivatives and their methods of use, including in the treatment of inflammatory conditions (see Abstract and Figures for chemical structures including ceramide, lactosylceramide and mammalian sphingomyelin). Paragraph 17 (Background of the Invention) describes how mice were fed diets with sphingomyelin supplemented foods. The authors disclose that such a compound is suited for the treatment of colitis (see paragraph 39, Summary of the Invention). Paragraph 541 provides sphingolipid conjugates. Paragraphs 641 provide terminally polar sphingolipids. Paragraph 543 describes antigens derived from immunized animals. Liotta et al teach using synthetic analogs of sphingosine throughout the entire document. Conjugates can be or include an enzyme for converting a prodrug into a drug (see Paragraph 555). The authors provide the same method steps comprising administering the same ingredient to the same population. Inherently, this would result in the same effects, including changes in cytokine responses, NKT cells or Th1/Th2 balance.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either **anticipation** or obviousness has been established.

In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

Thus, the claims above are rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 151, 157, 161-170, 184, 191 and 205 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liotta et al, Makowska et al (2000) and Tanguchi et al (cited in the IDS).

The teachings of Liotta et al is applied as discussed above. Liotta et al does not explicitly teach using CD1 receptor presenting cell, glucosylceramide or galactosylceramide, or food deprivation.

Liotta et al describe how sphingolipids are found in a number of foods, including wheat flour, potato and beans. It would have been obvious to the ordinary artisan to

deprive the subjects of any food before providing them with the sphingolipid supplemented food specific for treatment. One would have been motivated to do so in order to control the concentration of the sphingolipids administered as well as control the effect. There would have been a reasonable expectation given this practice widely practiced and commonly known. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Separately, Makowska et al examine the difference in the ligand specificity between CD1d-restricted T cells with limited and diverse T-cell receptor (TCR) repertoire. The author used multiple ceramides which are listed on page 72. They include alpha-glucosylceramide and beta-galactosylceramide. Table 3 provides the responsiveness of CD1-reactive hybridomas with diverse TCR to the differential ceramides presented on CD1-transfectants. Additionally, Figure 5 depicts the responsiveness of KT/23 hybridoma comprising Valpha14+. Note that the supernatants were harvested and examined for IL-2 content in a CTLL assay (see corresponding figure legend). In conclusion, the authors demonstrate that alpha-glucosylceramide in stimulating NKT cells (Valpha14+); see conclusions on page 77.

Taniguchi et al teach a treatment method in which glycosylceramides and derivatives are used as the active ingredients in activating NKT cells; this method serves as remedies for diseases and disorders, including ulcerative colitis (whole document). The structure of glucocerebroside is disclosed on page 3. Further, "antigen presenting cells treated with KRN 7000 showed a marked stimulative effect on Va24+

NKT cell proliferation in a manner dependent on the number of antigen-presenting cells" (page 18, lines 57-58, also see Figure 9 on page 36). Taniguchi et al disclose the use of autologous antigens in the following quote "an autologous mixed leukocyte reaction (MLR) was performed using these antigen-presenting cells as stimulator cells and autologous peripheral blood mononuclear cells as responder cells" (page 18, paragraph 98).

Thus, it would have been obvious to one of ordinary skill in the art to combine the teachings above in order to perform a method of administering an intermediary metabolite in combination with antigen presenting cells. More specifically, Makowska et al provide that alpha-glucosylceramide stimulates NKT cells and Taniguchi et al provides the method of using antigen-presenting cells. One would have been motivated to combine the teaching in order to modulate the IL-2 content of a subject. There would have been a reasonable expectation of success given the alpha-glucosylceramide effects are well-characterized by Makowska et al and administering antigen-presenting cells is commonly known. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 11, 43-45, 47-52, 54, 59-60, 75-76, 97, 109, 119-120, 124-126, 151, 157, 161-170, 184, 191 and 205 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim1-7 and 9-15 of copending Application No. 11/378, 941. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed towards administering the same compounds which induce the same effects (NKT cell modulation and cytokine production).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michelle Horning/
Examiner, Art Unit 1648

/Bruce Campell/
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